

Assessment of Severity of Ovine Smoke Inhalation Injury by Analysis of Computed Tomographic Scans

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Background: Our goal was to evaluate computed tomographic (CT) scans of the chest as a means of stratifying smoke inhalation injury (SII) severity.

Methods: Twenty anesthetized sheep underwent graded SII: group I, no smoke; group II, 5 smoke units; group III, 10 units; and group IV, 16 units. CT scans were obtained at 6, 12, and 24 hours after injury. Each quadrant of each slice was scored subjectively: 0 = normal, 1 = interstitial markings, 2 = ground-glass appearance, and 3 = consolidation. The sum of all scores was the radiologist's score (RADS) for

that scan. Computerized analysis of three-dimensional reconstructed scans was also performed, based on Hounsfield unit ranges: hyperinflated, -1,000 to -900; normal, -899 to -500; poorly aerated, -499 to -100; and nonaerated, -99 to +100. The fraction of abnormal lung tissue (FALT) was computed from poorly aerated, nonaerated, and total volumes. Mean gray-scale density (DENS) was also computed.

Results: SII resulted in severity- and time-related changes in oxygenation (alveolar-arterial gradient), ventilation (respiratory rate-pressure product), DENS,

FALT, and RADS. Ordinal logistic regression generated a predictive model for severity of injury ($r^2 = 0.623$, $p = 0.001$), retaining RADS at 24 hours and rejecting the other variables.

Conclusion: At 24 hours, CT scanning enabled SII severity stratification; qualitative evaluation (RADS) outperformed current semiautomated methods (DENS, FALT).

Key Words: Smoke inhalation injury, Lung, Adult respiratory distress syndrome, Sheep, Computed tomography, Radiograph.

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Smoke inhalation injury (SII), which occurs in approximately 20% to 30% of patients admitted to burn centers, frequently causes prolonged pulmonary dysfunction, increases the risk of pneumonia, and increases the probability of death by up to 20% over that predicted by age and burn size alone.¹ Early diagnosis of inhalation injury is important, to identify those patients who merit close intensive care unit (ICU) observation, prophylactic intubation, and transfer to facilities with special resources such as high-

frequency percussive ventilation. SII is suggested by factors such as a history of closed-space injury, facial burns, larger burn size, and advanced age.¹ However, no single physical or historical finding is sufficiently sensitive or specific for definitive diagnosis.² Thus, procedures such as flexible fiberoptic bronchoscopy³ or xenon-133 scanning⁴ are used to diagnose subglottic SII.

Although accurate, these procedures do not allow for grading of the severity of SII or for quantification of the percentage of parenchymal or airway involvement. Such a scoring system might permit more accurate triage of patients. Peitzman et al. used a chest radiographic scoring system to evaluate patients with severe inhalation injury and burns. The majority (84%) of patients in this study had chest radiographic findings by 48 hours after injury, and these findings correlated with deteriorating pulmonary function (increased extravascular lung water, increased shunt, or decreased compliance).⁵ However, this study involved patients with severe inhalation injury only and not with lesser degree of injury.

Brown et al. evaluated the utility of a chest radiograph score, the $\text{PaO}_2/\text{FiO}_2$ ratio (PFR), the peak inspiratory pressure, and a bronchoscopic score in predicting survival after SII. They found that the PFR was useful at admission, bronchoscopic scores were not significantly different, and the radiographic and pressure data became useful only after 1 week of hospitalization.⁶ Fitzpatrick et al. found the respiratory rate-pressure product (respiratory rate multiplied by peak inspiratory pressure) during days 0 to 2 to be an accurate

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(85.7%) predictor of survival in children with SII.⁷ Aside from these preliminary efforts to predict survival on the basis of admission respiratory data, no scoring system for SII severity presently exists.

In the last decade, data have been published demonstrating the utility of computed tomographic (CT) scans of the chest for quantifying the severity of the acute respiratory distress syndrome (ARDS).^{8–12} Although it is well known that admission chest radiographs are normal in the majority of patients with SII,¹³ Clark et al. in 1982 reported the superior sensitivity of CT scanning compared with either chest radiographs or xenon-133 lung scans for the early detection of severe SII in dogs.¹⁴ Thus, we hypothesized that current generation CT scanning would be capable of quantifying the severity of SII in an ovine model of graded injury.

MATERIALS AND METHODS

This study was approved by the institutional animal care and use committee. All animals were cared for in accordance with the guidelines set forth by the Animal Welfare Act and other federal statutes and regulations relating to animals and studies involving animals and by the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council. All animals were maintained in a facility approved by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Animal Preparation

Twenty 1- to 2-year-old neutered male sheep, from a commercially available, random source (*Ovis aeries*, Rambouillet X), weighing 24 to 33 kg, and free of antibodies to *Coxiella burnetti*, were used in the study. Animals were observed for 1 week in temperature-controlled, indoor runs; treated for parasites (1% ivermectin, 1 mL/75 lb); and fed commercial chow and water ad libitum. They were fasted for 24 hours before tracheostomy and instrumentation.

The day before smoke or sham-smoke exposure, the animals were anesthetized (ketamine 5 mg/kg intravenously [i.v.] and midazolam 0.275 mg/kg i.v.) and orotracheally intubated with a 7-mm (inside diameter) cuffed tube. Before transport of the animal to the operating room for instrumentation, a chest radiograph was obtained to exclude animals with active lung disease. Isoflurane (2–4%) was administered during instrumentation. A femoral artery was catheterized with a Silastic cannula; an external jugular vein was catheterized with an introducer sheath (8.5 Fr, American Edwards Laboratories, Inc., Irvine, CA), followed by an 8-Fr balloon-tipped pulmonary artery catheter; and open cystostomy and insertion of a urinary catheter were performed. A tracheostomy was performed, and a 9-mm, low-pressure, cuffed tracheostomy tube (Shiley, Mallinckrodt Medical TPI, Irvine, CA) was inserted. The animals were recovered overnight in an animal ICU.

Smoke Inhalation

The following day, animals were reanesthetized (sodium pentobarbital, 25 mg/kg i.v.). Once general anesthesia was confirmed, a neuromuscular blocking agent was given (pancuronium bromide, 0.03–0.04 mg/kg i.v.). These drugs were redosed, and an intravenous analgesic (buprenorphine, 0.005 mg/kg) was administered, whenever necessary. All animals remained anesthetized and mechanically ventilated for the remainder of the study; a Siemens 900C ventilator (Siemens-Elma, Solna, Sweden) was used. The animals were fasted, and maintenance intravenous fluid (5% dextrose in lactated Ringer's solution at 2 mL/kg/h) was given.

On the day of injury, each animal was randomized to one of four groups. Group I (control, n = 5) received no smoke, group II (mild, n = 5) received 5 units of smoke, group III (moderate, n = 5) received 10 units, and group IV (severe, n = 5) received 16 units.

A previously described method of causing SII was used, with slight modifications.¹⁵ Fifty grams of wood bark (Decorative Western Bark, Far West Forests, Inc., Tempe, AZ) was cut into 1-cm² chips and placed in a crucible furnace (Lindberg/BlueM Laboratory Furnace, model 56622, Asheville, NC). The firing chamber of the furnace was heated to 400°C. The chamber was supplied with desiccated air at 6.0 L/min, to support combustion and to facilitate flow of the smoke from the chamber into a 5.5-L Plexiglas reservoir. This reservoir also received 100% oxygen at 6 L/min, permitted the smoke to cool to ambient temperature, and facilitated mixing. Three minutes after initiation of burning, the smoke was drawn from the reservoir into a hand-operated piston and was delivered to the animal via its tracheostomy. The temperature of the smoke was measured just proximal to the tracheostomy tube using a thermistor-tipped pulmonary artery catheter. The tidal volume of each smoke breath was controlled by an adjustable stop on the piston set at 30 mL/kg. One unit of smoke was defined as five such breaths; each breath included a 7-second inspiratory hold. All animals received the same number of piston-driven tidal volumes regardless of the smoke dose. For example, the control animals received the same number of breaths, via the same apparatus, but without smoke.

Immediately after smoke exposure, arterial blood gas analysis was performed and the carboxyhemoglobin (COHb) level was measured by co-oximetry. Animals were moved back to the animal ICU, where they were housed in individual metabolic cages. Arterial blood pressure, heart rate, and peripheral oxygen saturation were continuously monitored. A rumen tube was placed for the rest of the study.

Ventilator Management

After SII, all animals were mechanically ventilated with 100% oxygen for 2 hours, regardless of severity of injury. Initial ventilator settings were as follows:

- Mode: pressure control
- Peak inspiratory pressure (PIP) above peak end-expiratory pressure (PEEP): sufficient to provide an inspired tidal volume of 10 mL/kg
- FiO_2 : 100% for 2 hours, then wean rapidly to 60%
- PEEP: 5 cm H_2O
- Respiratory rate: 15 breaths/min
- Inspiratory time: 25%

To limit barotrauma, ventilator management followed the following plan:

- Mode: no change
- PIP: adjust to maintain inspired tidal volume of 10 mL/kg, up to a maximum PIP of 40 cm H_2O . Then, permit hypercapnia as long as $\text{pH} > 7.1$
- FiO_2 : adjust to keep $\text{SpO}_2 > 91\%$ and $\text{PaO}_2 > 60$ mm Hg
- PEEP: no change until $\text{FiO}_2 = 100\%$, then increase up to

a maximum of 15 cm H_2O , to keep $\text{SpO}_2 > 91\%$ and $\text{PaO}_2 > 60$ mm Hg

- Respiratory rate: adjust to keep $\text{pH} > 7.1$, up to a maximum of 30 breaths/min

Changes in PEEP were minimized, and other available modalities (such as high-frequency percussive ventilation¹⁶) were not used, to avoid the possibly confounding effects of these maneuvers on lung CT scan appearance.

CT Scans

At 6, 12, and 24 hours after SII, CT scans of the chest were obtained. These times were selected on the basis of preliminary experience with severely injured animals, which suggested that CT scan changes might be detectable as early as 6 hours after injury in this group, and that some animals in this group might not survive 48 hours. Also, we sought to

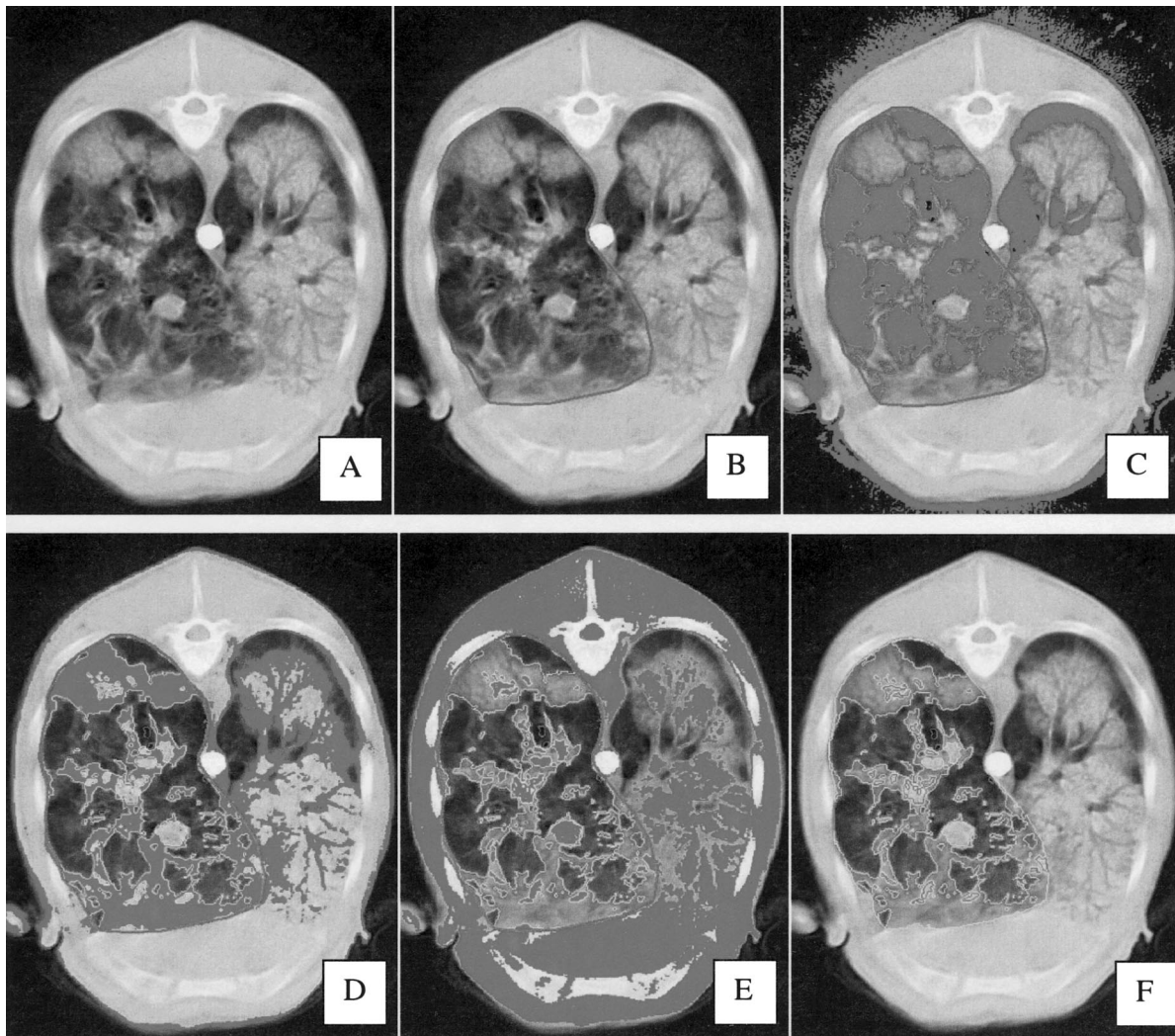


Fig. 1. Method of semiautomated CT scan analysis. (A) Original CT scan. (B) Manual selection of the region of interest, in this case the right lung. All subsequent analysis will be confined to this region. (C) Identification of pixels in the normally aerated HU range. (D) Identification of pixels in the poorly aerated HU range. (E) Identification of pixels in the nonaerated HU range. (F) Final appearance of scan. Hyperinflated areas, although present, occupied an insignificant percentage of the total lung volume in this study and are not shown.

determine whether CT scanning can detect early signs of SII severity, which would later be confirmed by the clinical course of the animals and by histology at the end of the 48-hour experimental period. A Picker PQS helical scanner (Picker, Dublin, Ireland) was used; this scanner underwent daily quality-control validation versus standard CT phantoms. During transport to the off-site CT scanning facility, animals were mechanically ventilated with a time-cycled, pressure-limited transport ventilator (Duotron, Percussionaire, Sandpoint, ID). The animals were placed in the ventral recumbent position on the scanner couch. A spiral technique was used, with contiguous 8-mm collimation, and the images were saved in native DICOM format. A thoracic radiologist, blinded to group membership and to time point, evaluated each scan and developed a scoring system for these evaluations. Each image slice was divided into four quadrants (i.e., right and left ventral and right and left dorsal). Each quadrant was given a numeric score: 0 = normal, 1 = interstitial markings, 2 = ground-glass opacification, and 3 = consolidation. The worst possible score was given to each quadrant, that is, the presence of a small area of consolidation in a quadrant yielded a score of 3, even if the remainder of the quadrant was not consolidated. This score was added across all quadrants and slices, to give the total radiologist's score (RADS) for the entire scan.

In addition, semiautomated analysis of the images using a software package, 3D-Doctor (Able Software Corp., Lexington, MA), was performed.¹⁷ This involved slice-by-slice assessment using the interactive segmentation function of the software. The pulmonary parenchyma was separated into four regions based on the Hounsfield unit (HU) ranges reported by Gattinoni et al.:¹² hyperinflated areas (−1,000 to −900 HU), normally aerated areas (−899 to −500 HU), poorly aerated areas (−499 to −100 HU), and nonaerated areas (−99 to +100 HU) were defined by the software in each of the slices for each of the lungs (Fig. 1). The software also analyzed each scan with respect to the total lung volume and the

gray-scale histogram; it calculated the mean value of the gray-scale histogram, called the "mean gray-scale density" (DENS) of the lung as a whole. The "fraction of abnormal lung tissue" (FALT) was calculated as the sum of the volumes of poorly aerated and of nonaerated lung, divided by the total lung volume. Three-dimensional reconstructed views of the lungs were also generated, allowing the display in different colors of the lung volumes categorized as previously mentioned. The operator performing the software analysis was blinded to group assignment.

Cardiopulmonary Data

Before injury and 6, 12, 18, 24, 36, and 48 hours after injury, cardiopulmonary variables and blood gases were measured. Pulmonary artery wedge pressure, central venous pres-

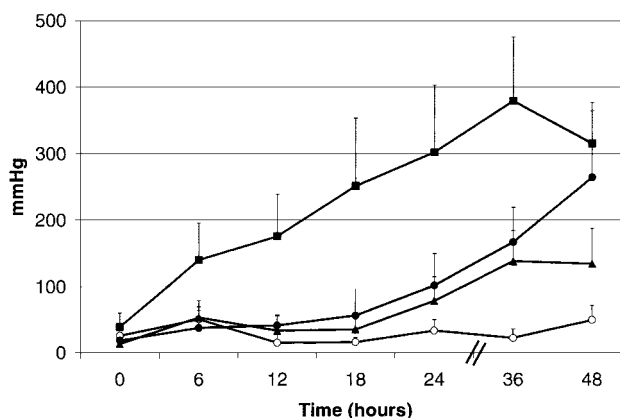


Fig. 3. Arterial-alveolar gradient. Changes over time ($p < 0.001$) and between groups ($p < 0.041$) were significant. Differences were present between the control and severe groups at each time point beginning with hour 12. ■, Severe group; ▲, moderate group; ●, mild group; ○, control group.

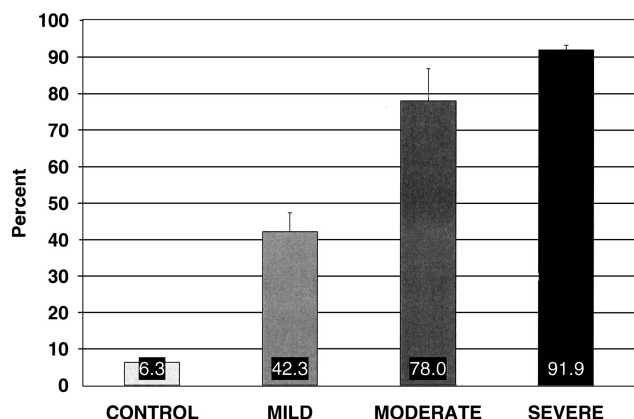


Fig. 2. Arterial carboxyhemoglobin levels (percent) immediately after smoke exposure. There was a significant difference between each injured group and the control group ($p < 0.001$).

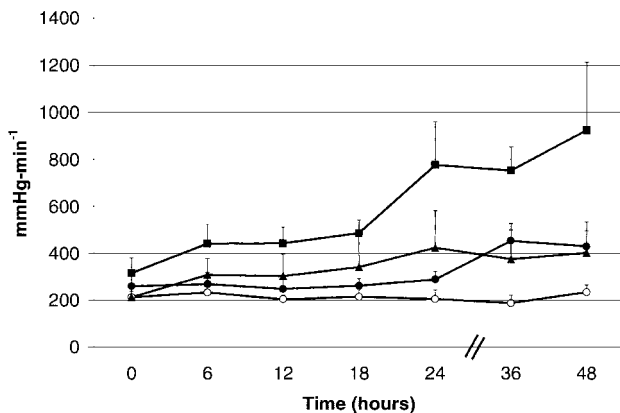


Fig. 4. Respiratory rate-pressure product. Changes over time ($p = 0.007$) and between groups ($p = 0.007$) were significant. Differences were present between the control and severe groups at each time point beginning with hour 12. ■, Severe group; ▲, moderate group; ●, mild group; ○, control group.

sure, and mean arterial pressure were measured using a pressure monitor (Model 78354A, Hewlett-Packard Company, Waltham, MA). Cardiac output was measured by the thermodilution technique (Cardiac Output Computer Model 9520A, American Edwards Laboratories, Santa Ana, CA). Blood-gas analysis was performed using an IL1303 pH/blood gas analyzer and an IL482 Co-oximeter (Instrumentation Laboratories, Inc., Lexington, MA). The respiratory rate-pressure product (RPP) was calculated as PIP multiplied by respiratory rate.

Postmortem Examinations

Forty-eight hours after injury, animals were killed by means of a standard veterinary solution, which provides an overdose of sodium pentobarbital. Lung and trachea were excised for hematoxylin and eosin staining and light microscopic examination. Histologic grading of tracheal and pulmonary injury was performed using the previously described

scoring system.¹⁸ The tracheal damage score is as follows: grade 0, normal; grade 1, some loss of cilia, loss of apical epithelium; grade 2, marked attenuation of epithelium or a single layer of epithelium; grade 3, <50% segmental/focal ulceration of epithelium (or covered by serocellular/mucocellular cast); and grade 4, >50% ulceration of epithelium. Parenchymal damage was evaluated at the apical, cardiac, and diaphragmatic lobes of both lungs. The pulmonary damage score is as follows: grade 0, normal; grade 1, minimal or mildly thickened alveolar septae, a few inflammatory cells or a small, single focus of inflammatory cells; grade 2, multifocal areas with increased inflammatory cells in alveolar septae and in alveoli; grade 3, diffuse inflammation and/or edema that affects <50% of the section; and grade 4, diffuse inflammation and/or edema that affects >50% of the section.

Parenchymal samples from right and left lung were excised for the determination of the blood-free wet-to-dry lung ratio using the method described previously.¹⁹ Briefly, bilateral apical, cardiac, and diaphragmatic tissue samples were

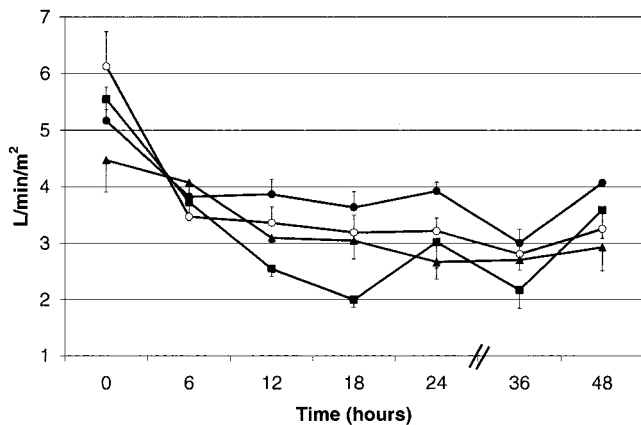


Fig. 5. Cardiac index. This variable changed over time ($p < 0.001$), but differences between groups were not significant. ■, Severe group; ▲, moderate group; ●, mild group; ○, control group.

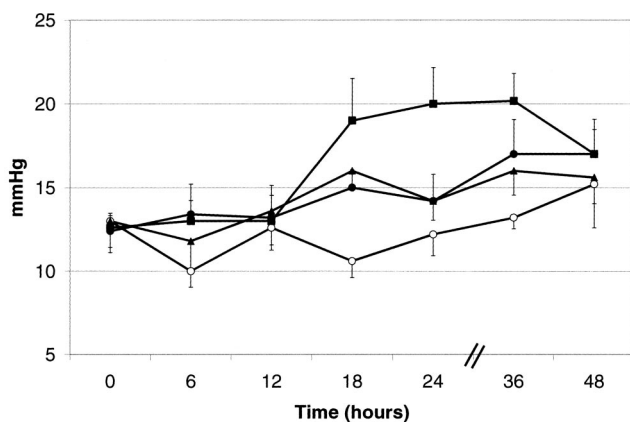


Fig. 6. Mean pulmonary artery pressure. Changes over time were significant ($p = 0.002$), but the apparent differences between groups during the latter half of the study were not. ■, Severe group; ▲, moderate group; ●, mild group; ○, control group.

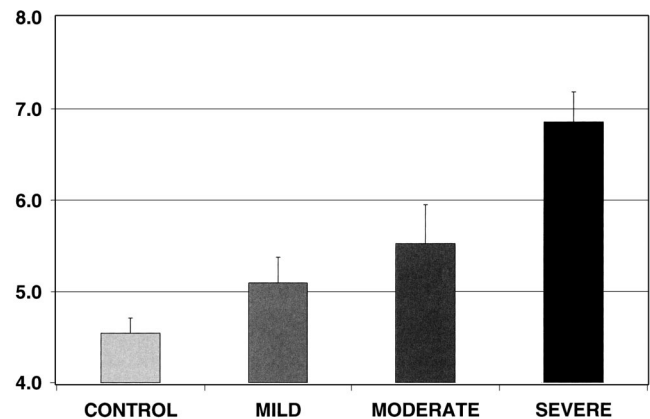


Fig. 7. Blood-free wet-to-dry ratios. The control group differed from the severe group ($p = 0.001$).

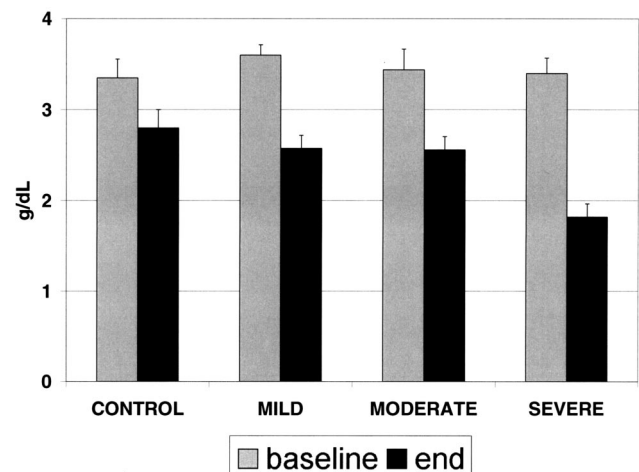


Fig. 8. Serum albumin. Decreases in serum albumin level appeared to correspond to injury severity, and the severe group differed from the control group at the end of the study ($p = 0.003$).

homogenized with an identical weight of distilled water. Samples of the homogenate and venous blood were weighed and dried at 80°C for 48 hours. Dry weights were measured and the wet-to-dry ratios of the homogenate and blood were calculated. A sample of the homogenate and blood, 20 μ L of the homogenate supernatant, or the diluted blood was added to 2.5 mL of Drabkin solution. The absorbance of both solutions was measured spectrophotometrically at 540 nm. From these data, the blood-free wet-to-dry ratio was calculated.

Statistical Analysis

Data analysis used SPSS version 10.1 (SPSS, Inc., Chicago, IL). As appropriate, one-way or repeated-measures analysis of variance was performed, with severity of injury as the between-groups factor. Post hoc Dunnett *t* tests were performed to compare each injured group to the control group at various time points. Because of the relatively small sample size, post hoc tests for changes over time were, in general, not performed. Ordinal data, specifically, the histologic score, were analyzed using the Kruskal-Wallis *H* test and post hoc

Mann-Whitney *U* tests, with correction for multiple non-orthogonal comparisons. Bivariate and multivariate linear regression was performed; also, ordinal logistic regression (PLUM procedure) was used to evaluate candidate independent predictors for severity of injury. Significance was accepted at $p < 0.05$. Data are presented as means \pm SEM, unless otherwise noted.

RESULTS

This study required approximately 1,500 total hours of animal intensive care. Two animals in the severe group were killed at hours 29 and 36, because of terminal pulmonary failure (inability to maintain a P_{aO_2} of 60 mm Hg, despite $F_{IO_2} = 100\%$ and PEEP = 15 cm H_2O). One animal in the mild group died at hour 36, because of airway obstruction. The rest of the animals lived until the completion of the 48-hour study.

Arterial COHb levels measured immediately after SII corresponded in stepwise fashion to smoke dose, showing a significant difference among groups ($p < 0.001$) and between each injured group and the control group ($p < 0.001$) (Fig. 2).

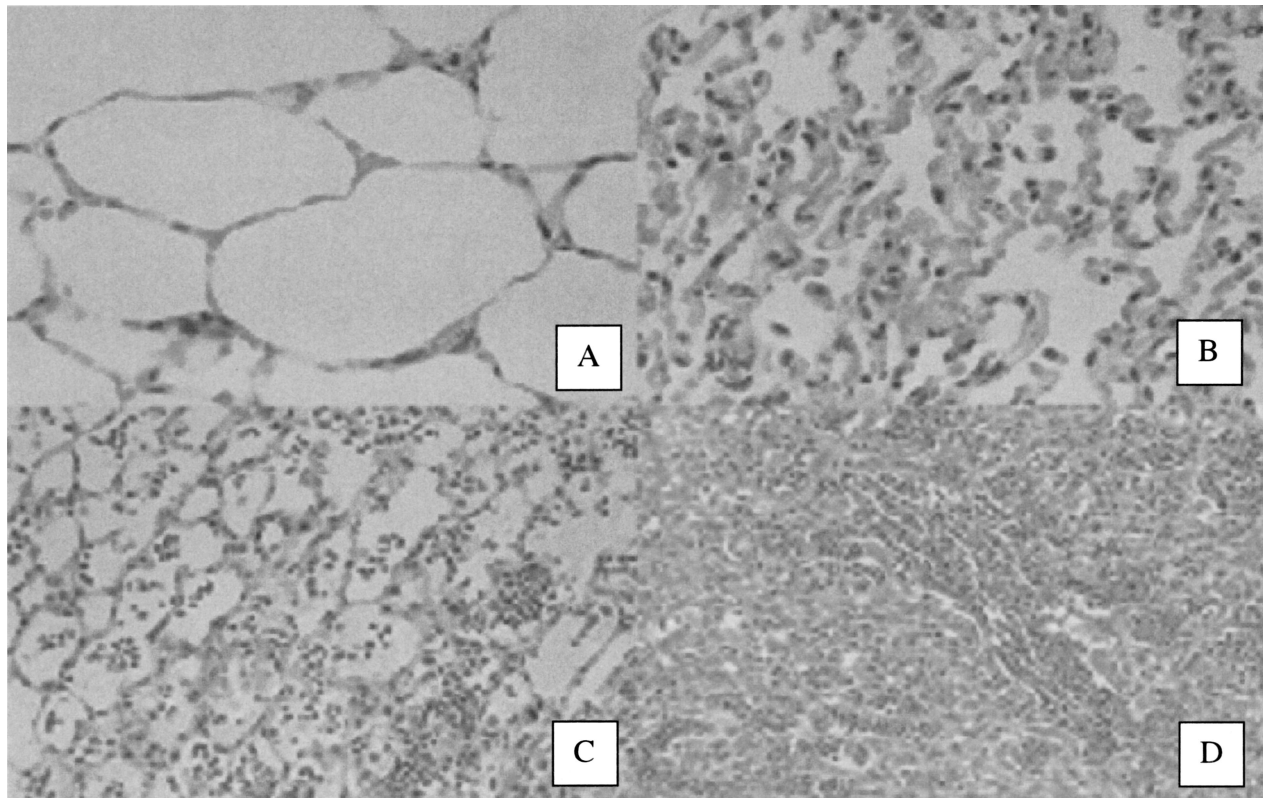


Fig. 9. Lung histology, 48 hours after SII. (A) Control group (hematoxylin and eosin (H&E); original magnification, $\times 400$). (B) Mild group (H&E; original magnification, $\times 400$). There is multifocal, minimal to moderate thickening of the alveolar septa with few intra-alveolar inflammatory cells. (C) Moderate group (H&E; original magnification, $\times 200$). There is diffuse mild to moderate thickening of alveolar septa with multifocal, intra-alveolar fibrin, edema, and aggregates of large numbers of inflammatory cells, predominantly neutrophils with small numbers of histiocytes. (D) Severe group (H&E; original magnification, $\times 200$). There is diffuse marked thickening of alveolar septa with multifocal, mild type II pneumocyte hyperplasia, and diffuse intra-alveolar aggregates of neutrophils admixed with small numbers of histiocytes, lymphocytes, and fibrin.

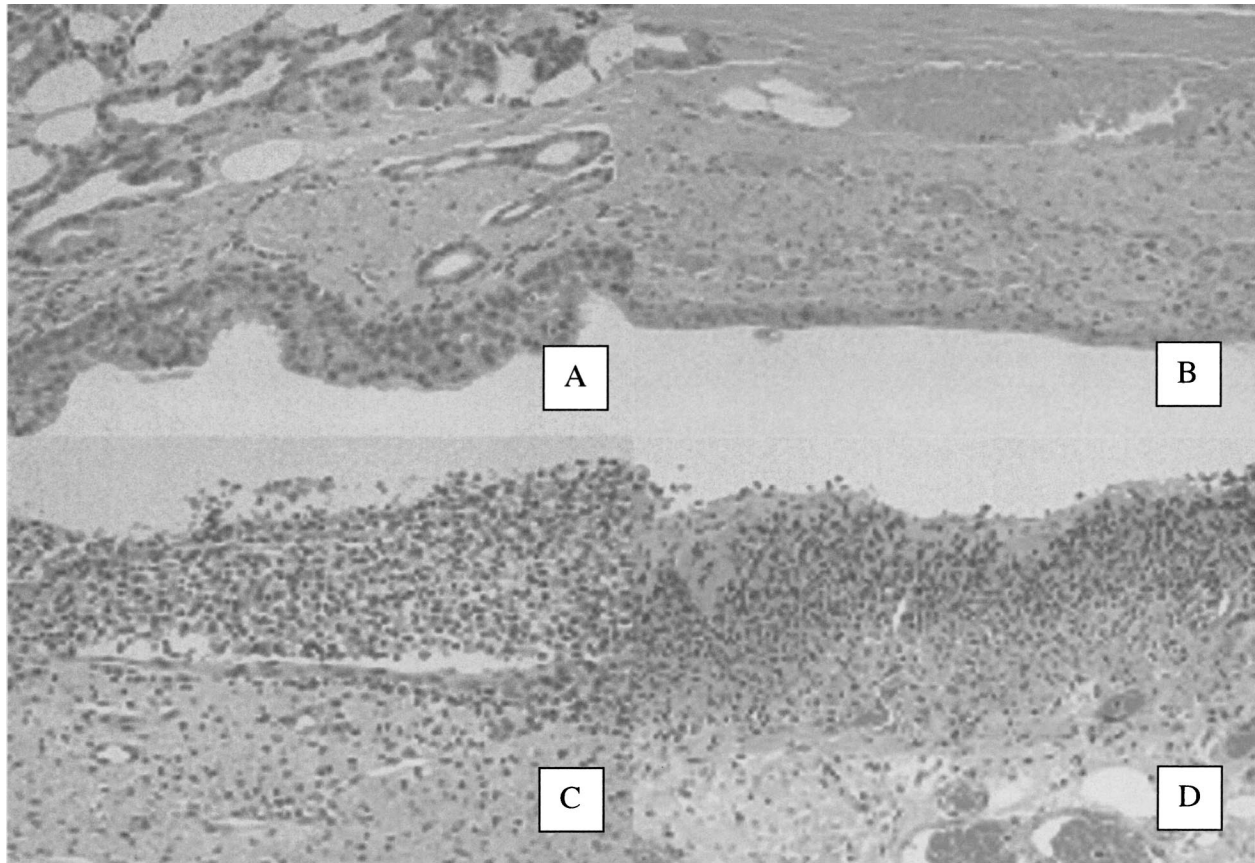


Fig. 10. Trachea histology, 48 hours after SII (H&E; original magnification, $\times 200$). (A) Control group. (B) Mild group. There is diffuse loss of cilia with multifocal attenuation of epithelium. Multifocally, there is submucosal transmigration of small numbers of neutrophils. (C) Moderate group. There is diffuse loss of cilia and marked attenuation of epithelium. Multifocally, the epithelium is ulcerated and associated with an overlying mat of fibrin admixed with large numbers of inflammatory cells and proteinaceous debris. (D) Severe group. There is diffuse necrosis of epithelium and, multifocally, of underlying submucosa. A mat of fibrin, necrotic debris, and admixed inflammatory cells overlays the necrotic epithelium.

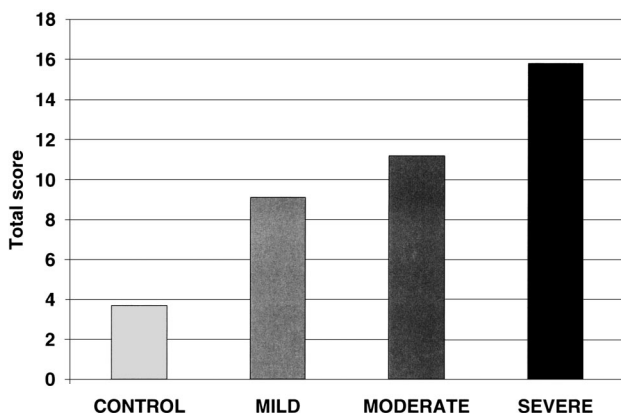


Fig. 11. Histologic score at 48 hours (mean ranks), consisting of the sum of all six lung scores plus one tracheal score. There was a stepwise increase in the severity of injury, which corresponded to smoke dose; the control group differed from the severe group ($p = 0.024$).

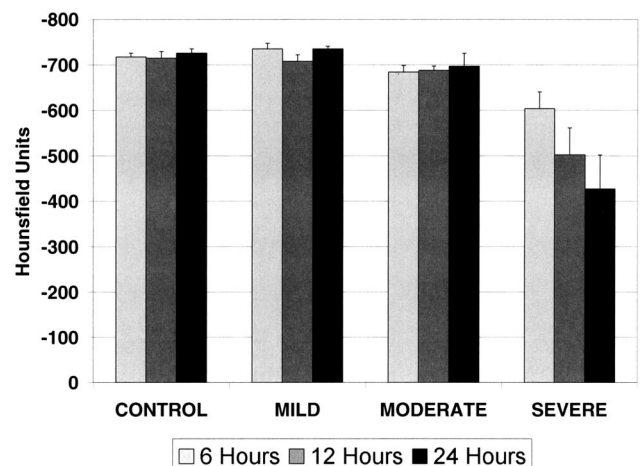


Fig. 12. CT scans: results of computerized analysis. Mean gray-scale density (DENS). There were significant differences between control and severe sheep at all three time points (at 6 hours, $p = 0.004$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$).

The alveolar-arterial gradient (AaO_2) changed over time within groups ($p < 0.001$) and between groups ($p = 0.04$). The differences were significant between the control and severe groups at hours 12 through 48 (Fig. 3). The PFR changed over time ($p < 0.001$), but between-group differences were not significant (data not shown). (It is noteworthy that the severe group achieved an ARDS level PFR of 183.0 ± 46.8 at the 24-hour mark.) Likewise, the RPP varied over time ($p < 0.001$) and between groups ($p = 0.007$), with significant differences between the control and severe groups at hours 12 through 48 (Fig. 4). Cardiac index ($p < 0.001$) (Fig. 5) and mean pulmonary artery pressure ($p = 0.002$) (Fig. 6) varied over time, but differences between groups were not significant. Blood-free wet-to-dry ratios, similar to COHb levels, showed stepwise increases with severity of injury; the severe group differed from the control group ($p = 0.001$) (Fig. 7). Concomitantly, serum albumin levels, measured at 0 and 48 hours, decreased in all groups and appeared to decrease more as injury severity worsened. Control and severe groups differed significantly at the end of the study

(Fig. 8). Similar changes occurred in total protein levels (data not shown).

Typical histologic findings are shown in Figures 9 and 10. The histologic score at 48 hours, shown in Figure 11, corresponded with smoke dose; the severe group differed significantly from the control group ($p = 0.024$).

CT Scans

DENS differed over time ($p = 0.002$) and between groups ($p < 0.001$). As can be seen (Fig. 12), the differences between control and severe sheep at all three time points (at 6 hours, $p = 0.004$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$) were significant. Figure 13 depicts changes in the distribution of lung aeration (HU ranges) determined by semiautomated analysis. These data are summarized in Figure 14, which shows the FALT. FALT varied over time ($p = 0.003$) and between groups ($p = 0.001$). The severe group differed from the control group at all three time points (at 6 hours, $p = 0.01$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$). Figure 15 shows the results of the RADS. There

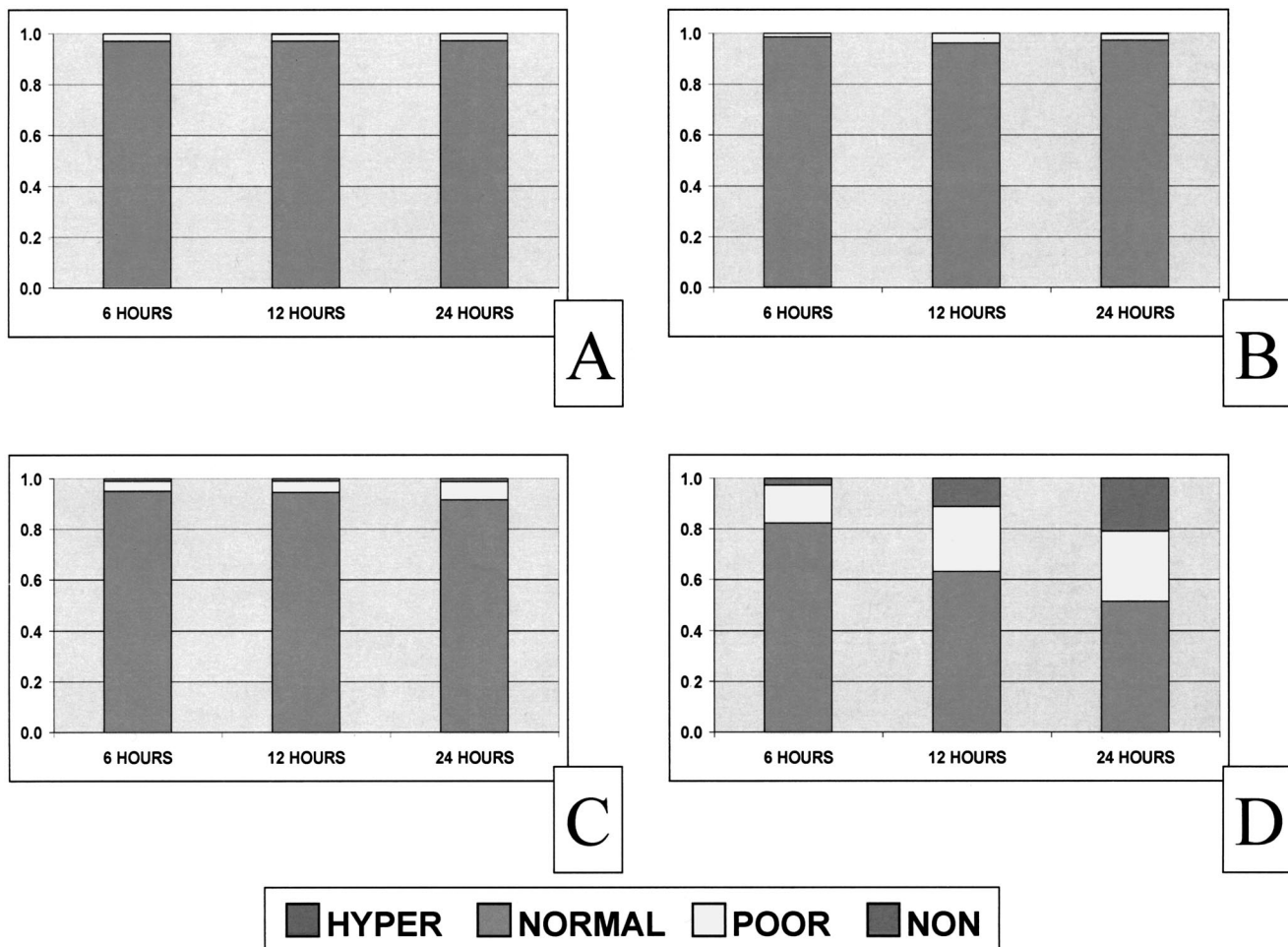


Fig. 13. CT scans: results of computerized analysis. Changes in distribution of aeration ranges over time. (A) Control group. (B) Mild group. (C) Moderate group. (D) Severe group. Only the severe group demonstrated striking changes over time. Note that hyperinflated lung tissue was not present in significant amounts in any group.

were significant changes over time ($p < 0.001$) and between groups ($p < 0.001$). Severe and control groups differed at all three time points (at 6 hours, $p = 0.027$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$). By 24 hours after injury, a clearcut progression in RADS, corresponding to severity of injury and not present for DENS or FALT, is evident.

Thus, it appeared that RADS was more sensitive to relatively minor changes in radiographic morphology. This is

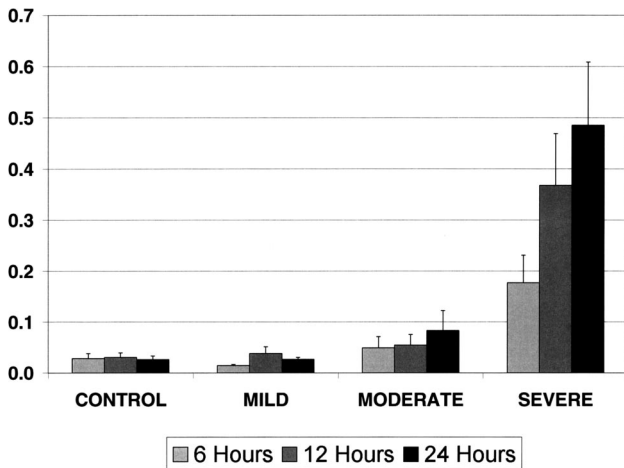


Fig. 14. CT scans: results of computerized analysis. Fraction of abnormal lung tissue (FALT), calculated as the sum of the volumes of nonaerated and poorly aerated lung, divided by the total lung volume. FALT varied over time ($p = 0.003$) and between groups ($p = 0.001$). The severe group differed from the control group at all three time points (at 6 hours, $p = 0.01$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$).

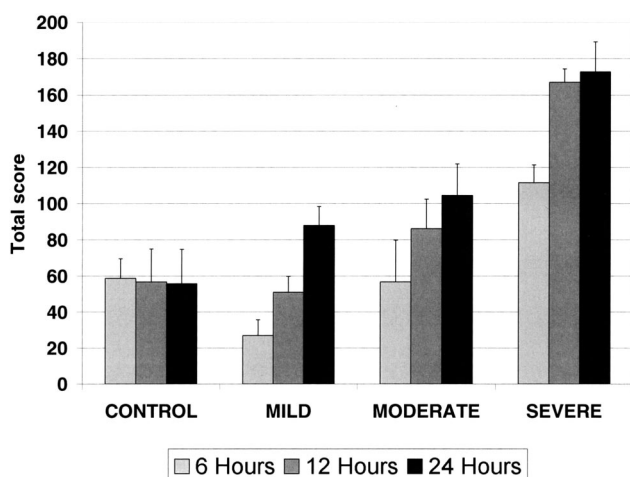


Fig. 15. CT scans: results of radiologist's score (RADS). There were significant changes over time ($p < 0.001$) and between groups ($p < 0.001$). Severe and control groups differed at all three time points (at 6 hours, $p = 0.027$; at 12 hours, $p < 0.001$; and at 24 hours, $p < 0.001$).

confirmed by Figure 16, which depicts regression of RADS versus FALT. In contrast, the relationship between RADS and DENS was reasonably linear ($r^2 = 0.578$, $p < 0.001$; data not shown). Examining the relationship between the CT scan variables and oxygenation at all time points (Fig. 17), we found that RADS correlated better with $AaDO_2$ than did the other variables. It was possible, however, to incorporate all three variables into a multivariate linear regression equation with $AaDO_2$ as the dependent variable ($r^2 = 0.469$, $p < 0.001$; FALT, $p = 0.039$; DENS, $p = 0.081$; RADS, $p = 0.005$). By contrast, only RADS was retained in a model with RPP as the dependent variable ($r^2 = 0.256$, $p < 0.001$).

Ordinal logistic regression was used to evaluate candidate independent variables with respect to the ordinal dependent variable, severity of smoke dose (control/mild/moderate/severe). The three CT scan variables and the $AaDO_2$ for each time point (6, 12, and 24 hours) were entered, and only RADS at 24 hours was retained in the model ($p = 0.001$, Cox and Snell pseudo- $r^2 = 0.623$).

DISCUSSION

The model of graded SII used in this study caused cardiopulmonary and histologic changes similar to those previously described from this Institute and elsewhere.²⁰⁻²² These changes were present both at the beginning of the study, in the form of COHb levels, and at the end of the study, in the histologic scoring system results and blood-free wet-to-dry ratios. Interestingly, the same gradation was not consistently seen during the study in the physiologic variables. Thus, no differences were seen in cardiac index between groups, and changes in $AaDO_2$, PFR, and RPP did not perfectly follow severity of initial injury. Similar results were reported by

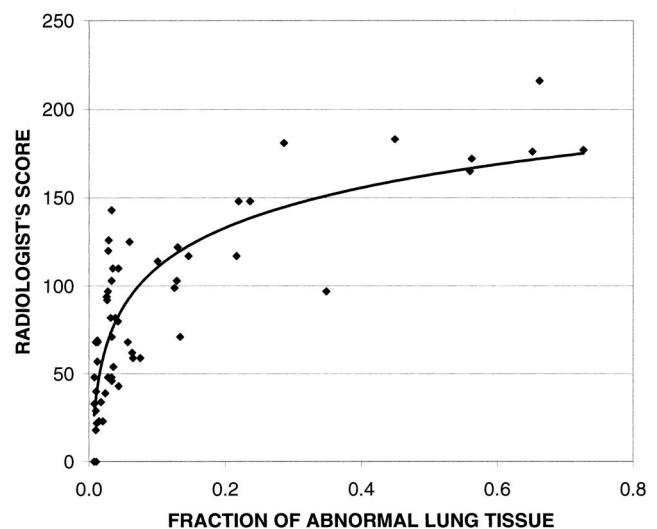


Fig. 16. CT scans: comparison of the fraction of abnormal lung tissue (FALT) derived from computerized analysis, and the radiologist's score (RADS). RADS appeared to make finer distinctions at the low end of FALT.

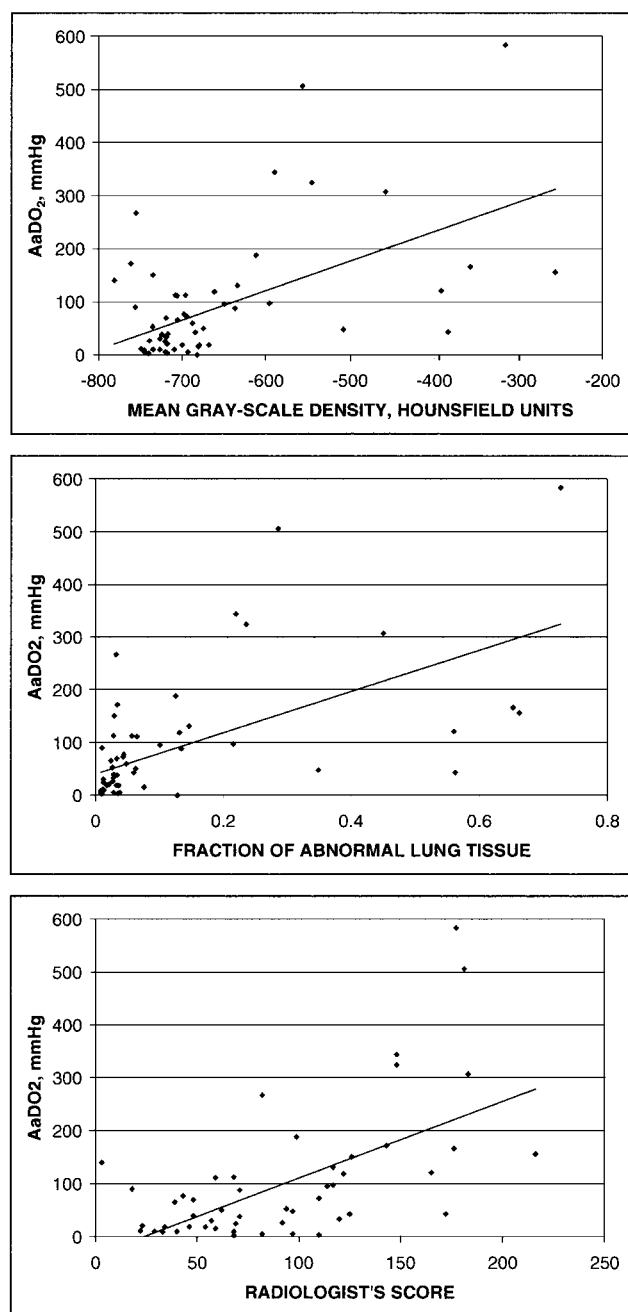


Fig. 17. Linear regression of DENS ($r^2 = 0.287$, $p < 0.001$), FALT ($r^2 = 0.348$, $p < 0.001$), and RADS ($r^2 = 0.379$, $p < 0.001$) vs. AaDO₂. Correlation of RADS with this index of oxygenation was superior to that of the two computer-generated variables.

Shimazu et al. for sheep exposed to smoke generated by combustion of hospital underpads (containing polyethylene, wood pulp, and cellulose fabric): significant changes in Pao₂ and cardiac index were not seen until a certain threshold smoke dose had been reached.²⁰ Thus, it appears likely—as one would expect—that the local, anatomic effects of SII occur at lower doses than do the systemic manifestations of pulmonary injury.

The principal finding in the present study is that a CT scan scoring system, applied by an expert analyst at 24 hours after injury, is capable of accurate classification of animals according to severity of initial smoke dose. Furthermore, this scoring system is superior to current computerized image analysis methods. To date, one other article has described the use of CT scanning in the diagnosis of smoke inhalation. In 1982, Clark et al. reported the superior sensitivity of CT scans in comparison with chest radiographs and xenon-133 lung scans for the detection of pulmonary lesions within 2 hours of a severe SII in dogs.¹⁴

Other authors have used various CT scan findings to determine severity of injury and to predict clinical outcomes in nonsmoke pulmonary injuries. In patients with ARDS of various causes, Owens et al. reported a correlation between the Murray Lung Injury Score (incorporating Fio₂, PEEP, compliance, and a chest radiograph score) and the fractional volume of abnormal lung as measured by a radiologist.²³ Miller et al. determined that a pulmonary contusion volume in excess of 20% of the total lung volume greatly increased the risk of development of ARDS in trauma patients; other variables, such as the PFR, were not useful in this regard.²⁴

Several authors have devised subjective scoring systems for the analysis of CT scans in ARDS. Gattinoni et al. compared the CT scans of patients with early, intermediate, and late ARDS; they subjectively scored the scans according to density as hazy, patchy, or compact, and noted no changes over time.¹¹ Scillia et al., in a study of canine oleic acid injury, used a score that grades the severity and the extent of ground-glass opacification. They also quantified mean gray-scale density. Mean gray-scale density correlated well with the subjective score in this study ($r^2 = 0.88$).²⁵ Goodman et al., comparing scans of patients with differing causes for ARDS, graded each lung section as demonstrating normal architecture, ground-glass opacification, or consolidation.²⁶ The present study adds an additional category of “increased interstitial markings” between normal and ground-glass opacification. The clinical utility and interrater reliability of the revised score described in the present study have not been determined. However, it appears that it is sensitive to relatively mild changes in pulmonary morphology, which do not cause significant increases in DENS or FALT, but which nevertheless indicate the presence of underlying lung injury.

The concept that an expert analyst may be sensitive to subtle morphologic changes that precede overt increases in lung density is reminiscent of work by Chrysopoulou et al., who analyzed the chest radiographs of patients with thermal injury but without inhalation injury. These authors found—for that subset of patients with sepsis—that increases in a chest radiographic score precede increases in extravascular lung water measured by dual-indicator dilution. However, this did not hold true for those patients without infection.²⁷

The potential utility of CT scanning in the treatment of patients with SII is not limited to determination of severity of injury. For example, Gattinoni et al. have used the CT scan to

establish the regional inhomogeneity of lung density distribution in ARDS. They, and others, have described the response to maneuvers such as PEEP, PIP, and prone positioning.^{12,28,29} In patients with SII, the opportunity now exists to use the CT scan to characterize the effect of interventions such as high-frequency percussive ventilation (Volumetric Diffusive Respiration, Percussionaire, Sandpoint, ID)—increasingly used for the treatment of SII in burn centers—on lung aeration.

CONCLUSION

We have found that a subjective score of the severity of CT scan changes seen 24 hours after injury accurately classified animals according to severity of initial smoke dose. The clinical applicability of this score to outcome prediction remains to be determined.

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DISCUSSION

Dr. Nicholas Namias (Miami Beach, Florida): Dr. Park and associates have added to the wealth of knowledge in burn care already given to us by the U.S. Army's Institute for Surgical Research. They have used an established model of inhalation injury in sheep, creating varying degrees of lung injury and have attempted to devise a scoring system to stratify the severity of lung injury.

They have included respiratory and nonrespiratory markers of severity as well as histology. The study is of straightforward design and elegant execution.

I have several questions and constructive criticisms. Dr. Park, please don't feel compelled to answer all of the questions regarding the procedural details, but please do expand on the conceptual question I pose first.

The premise of the study, as stated in the article, is that early diagnosis is important to identify those patients who merit ICU observation, prophylactic intubation, and transfer to specialized facilities. I think this premise is flawed.

Who is the patient in whom the suspicion of inhalation is so high that you would obtain a CT scan but then triage the patient to the ward because the CT scan is negative? Who is the patient who is doing physiologically well, without respiratory embarrassment or another indication for airway protection, whom you would intubate because the CT scan is positive?

Finally, on this point, do you really think that nonspecialized centers will be able to assign a RADS, as you describe, to determine who should go to a specialized center? I promise you that the emergency rooms in South Florida don't need a CT scan with a RADS to decide they want to send their inhalation patients to my burn center.

You also state that the CT scan-based scoring system would be a useful triage tool in a mass casualty incident. To the contrary, in a real mass casualty incident, resource-intensive modalities rapidly become overwhelmed and the real triage tools become the eyes, ears, and hands of the most experienced surgeon on the team. Please do comment on this point.

I think what you have developed is an elegant research tool but not a clinical tool. As far as procedural details go, first, why did the mild, moderate, and severe groups get 5, 10, and 16 units of smoke and not 5, 10, and 15 units of smoke?

Second, will the CT scan findings after inhalation of a burning house be similar to the findings after the inhalation of burning tree bark? Third, if the ventilator was managed to give 10-mL/kg breaths, why were the smoke breaths 30 mL/kg?

Fourth, why was increasing PEEP withheld until the FIO_2 reached 100%? Perhaps earlier use of PEEP would recruit alveoli and reverse the CT scan changes you found. Fifth, why was the PEEP limited to a maximum of 15 cm H_2O ? I congratulate the authors on a well-done experiment that will make a significant contribution in the arena of burn research, and I thank the Association for the privilege of the floor.

Dr. Philip S. Barie (New York, New York): I congratulate you, Major Park, on an innovative study, well performed and well presented. I have two questions. First, we all have had the experience clinically of a seemingly discrepant physiology and radiologic appearance. In fact, it is well known that the radiologic markers of acute lung injury can be delayed in their resolution long beyond the patient's clinical improvement, and so I wonder whether you have considered

that in your analysis and correlated your CT scan findings with some more relevant physiologic markers.

Specifically, I wonder about lung water. Having worked in this field extensively in years past, I'm familiar with the crude methodology of wet-to-dry lung weight ratios and wonder whether you have correlated these with individual animals in any of your radiologic scores.

I wonder further why when imaging quantification of lung water was reported in *Science* in the late 1980s, you did not avail yourself of the opportunity to quantify lung water radiographically rather than making such a crude estimate. Thank you very much.

Dr. Jay A. Yelon (Manhasset, New York): I, too, enjoyed the article, and I want to echo some of Dr. Namias' concerns of the utility of this methodology in clinical practice. Certainly, from a research perspective, I find it interesting. I was wondering whether the authors compared it to the more standard approaches such as standard fiberoptic bronchoscopy, and also from a research perspective, whether they compared it to xenon-133 scanning, the two more accepted standards for diagnosing inhalation injury. Thank you.

Dr. Henry J. Schiller (Rochester, Minnesota): I'm just curious. I didn't see plateau pressures reported, and was there any correlation with plateau pressures and the CT scan findings at 6 hours?

Dr. Gregory A. Timberlake (Jackson, Mississippi): From the chair, previous work from your institution by Dr. Cioffi demonstrated that percussive ventilation was a much better mode for ventilating inhalation injured patients, yet I noticed that you did use a different mode. Could you tell us whether percussive ventilation is out the window? Why did you not use it? Thank you.

Dr. Myung S. Park (closing): Thank you very much for all of the questions. This is certainly the first study of its kind trying to evaluate whether or not CT scanning can actually have a role in evaluating patients with inhalation injury. This certainly is an animal model, and it needs to be validated in a clinical setting.

With regard to the utility of the radiologist's score that we discussed, it is merely for quantification. We wanted to at least establish that, when given different grades of smoke, there is somewhat of a quantifiable change on the CT scans.

Realistically, having worked with two different thoracic radiologists, it will take too long to sit down image by image, slice by slice, to assess. Rather, it will be more of a descriptive and qualitative assessment of the CT scan. The role of CT scanning in an inhalation injury patient still needs to be looked into.

Certainly, this is an animal model, and in the future, we hope that it can be used to assess and triage patients. However, going back to Dr. Namias' questions about patients who are clinically doing well but have an abnormal CT scan versus patients who are clinically doing poorly but have a normal CT scan, certainly you would use your clinical judgment to dictate patient care.

As far as why 5, 10, and 16 units of smoke were used versus 5, 10, and 15, these numbers were generated from previous research work out of our institution. Although 5, 10, and 15 would have been a better number, 5, 10, and 16 were based on previous work at our institution. In answering Dr. Timberlake's question, the high-frequency percussive ventilator

was not used in order to avoid the possible confounding effects of it on lung CT scan appearance. Fiberoptic bronchoscopy and Xenon-133 scans were not performed in this study to be used as comparisons. Finally, looking at volume of lung water radiographically is a great suggestion, and we will look into that. Thank you again for this opportunity to present our work.